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Intracerebroventricular administration of bacterial lipopolysaccharide prevents the development of acute experimental pancreatitis in the rat

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background: Lipopolysaccharides (LPS) are responsible for septic shock but low doses of LPS reduce pancreatic damage produced by caerulein-induced pancreatitis (CIP) in rats. Leptin, produced by adipocytes attenuates the severity of CIP. The aim of this study was to evaluate the effect of intracerebroventricular (i.c.v.) administration of LPS on CIP and plasma leptin level and to investigate the involvement of sensory nerves (SN) in the effects of LPS on CIP.

Material/Methods: CIP was produced by subcutaneous (s.c.) infusion of caerulein (25 μg/kg) to conscious rats. SN were deactivated with capsaicin (100 mg/kg s.c.). LPS (0.2, 2, or 20 μg/rat) were applied to the right cerebral ventricle 30 min prior to CIP.

Results: CIP was manifested by an increase in plasma levels of amylase, lipase, leptin and an anti-inflammatory interleukin 10 (IL-10), (by 400%, 1000%, 700% and 50%, respectively), confirmed by histological examination and accompanied by 40% reduction in pancreatic blood flow. Pretreatment of CIP rats with i.c.v. LPS resulted in significant reduction of CIP accompanied by dose-dependent increase in plasma levels of leptin and IL-10. Deactivation of SN, which by itself failed to affect CIP, completely reversed the beneficial effects of i.c.v. administration of LPS on CIP and reduced plasma leptin and IL-10 concentrations.

Conclusion: Pretreatment with LPS given i.c.v. prevents the development of caerulein-induced pancreatitis through the activation of SN and though the release of leptin.

Key words: lipopolysaccharide • leptin • caerulein-induced pancreatitis • sensory nerves

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BACKGROUND

Lipopolysaccharides (LPS, endotoxin) are a component of the cellular wall of Gram-negative bacteria [1]. They arouse interest due to their ability to stimulate immune cells and to activate tissue inflammatory factors [2,3]. Massive release of LPS may lead to septic shock and multiorgan failure (MOF), and endotoxemia complicating acute pancreatitis is a poor prognostic factor and may reflect fatal course of this disease [4–7]. Bacterial endotoxins may also induce pancreatitis by themselves [8].

Recent studies have demonstrated that in contrast to harmful effects exerted by high concentrations of bacterial LPS, small doses of endotoxins may alleviate inflammatory states in the organ. The administration of low-dose LPS blunted pancreatic injury in the course of acute experimental pancreatitis in rats, and endotoxins in trace doses limited the development of acute gastric ulcers [9–11]. Favorable effects of LPS seems to be associated with activation of nitric oxide synthase (NOS) and increased generation of nitric oxide (NO). Pretreatment with low dose of LPS improves the blood flow through the organ, upregulates the cyclooxygenases (COX) and increased biosynthesis of prostaglandins [10,11].

The protective effects of LPS may also occur through activation of other less understood mechanisms or intracellular factors such as heat shock proteins which should increase under the influence of LPS [12]. LPS are able to release leptin [13–15] and available evidence shows that leptin has a protective effect on the stomach and pancreas by modifying the production of cytokines and activating NO generation and biosynthesis of prostaglandins [16–19]. Experimental studies have indicated that anti-inflammatory effects of leptin are closely correlated with the activation of sensory nerves, because chemical deactivation of these nerves almost completely reversed the protective effects of leptin on the stomach and pancreas [20]. Sensory nerve (SN) fibers are sensitive to neurotoxin capsaicin, which induces reversible inactivation of these nerves and is used in experimental studies to identify the role of sensory nerves in the mechanisms regulating the activity of the digestive system [20].

Our previous studies have demonstrated that leptin is able to protect gastric mucosa and the pancreas against injury not only following its peripheral administration but also when it was given by the intracerebroventricular route [16,17,19,20]. Central administration of such hormones as dopamine, secretin or CGRP alters the exocrine function of the pancreas [21–23]. So far no studies have been performed on the effect of centrally administered substances that affect leptin release in acute pancreatitis.

The purpose of our study was: 1. to investigate the effect of LPS, obtained from Escherichia coli and applied intracerebroventricularly, on the course of acute caerulein-induced pancreatitis (CIP) in rats and 2. to clarify the role of SN and leptin in the central effect of endotoxin on the pancreas subjected to CIP.

MATERIAL AND METHODS

LPS from *Escherichia coli*, serotype 0127: BS and capsaicin were obtained from Sigma (St. Louis, MO, USA), caerulein (Takus) from Farmacia GmbH (Erlangen, Germany).

Wistar rats weighing about 200 g were used. The animals were kept in cages, fed with standard food and water ad libitum. Feeding was discontinued 18 hours prior to the start of the experiments.

The study protocol was approved by the Ethics Committee on Animal Experiments of the Jagiellonian University.

Acute caerulein-induced pancreatitis (CIP) was provoked by caerulein in 5-hour subcutaneous (s.c.) infusion at a dose of 5 μg/kg-h. Caerulein was dissolved in 0.9% physiological saline and administered at a rate of 1 ml/h. Control animals were infused with vehicle saline for 5 h.

LPS at a dose of 0.2, 2 or 20 μg/rat, dissolved in 20 μl of 0.9% saline was given to the right cerebral ventricle (i.c.v.) as described previously [19, 20]. LPS was applied as a bolus 30 min before the onset of pancreatitis-inducing infusion of caerulein, or saline in the control tests. For intracerebroventricular administration of LPS, the rats were briefly anesthetized with ether. A midline incision was made on the head exposing the skull and its sutures. The skull was pierced with a fine sharp needle at a site 2.5 mm to the sagittal and coronal sutures to administer LPS or saline. The efficacy of intracerebroventricular administration of LPS was checked by an injection of 20 μl of 0.2% toluidine blue.

Each animal group received a different dose of LPS and the control animals – normal saline. Each control group consisted of 6–8 animals.

The animals were randomly subdivided into two large groups. Group I consisted of animals with intact sensory nerves. Group II consisted of animals in whom sensory nerves were deactivated with capsaicin. Capsaicin was applied at a dose of 100 mg/kg s.c. over 3 days, 7 days prior to study. Both large groups were further subdivided into subgroups to receive: 1) saline in 5-h s.c. infusion, 2) caerulein at dose of 5 μg/kg-h dissolved in saline at 5-h s.c. infusion to induce CIP, 3) LPS i.c.v. at a dose of 0.2 μg/rat followed by a 5-h s.c. infusion of saline, 4) LPS i.c.v. at a dose of 2 μg/rat followed by 5-h s.c. infusion of saline, 5) LPS i.c.v. at a dose of 20 μg/rat followed by a 5-h s.c. infusion of saline, 6) LPS i.c.v. at a dose of 0.2 μg/rat followed by a 5-h s.c. infusion of caerulein, 7) LPS i.c.v. at a dose of 2 μg/rat followed by a 5-h s.c. infusion of caerulein, 8) LPS i.c.v. at a dose of 20 μg/rat followed 5-h s.c. infusion of caerulein.

Following 5-h infusion of caerulein, or saline, the animals were anesthetized with Vetbutal (0.5 ml/kg i.p.), and then the abdominal cavity was opened. Pancreatic blood flow was measured by a laser Doppler flowmeter

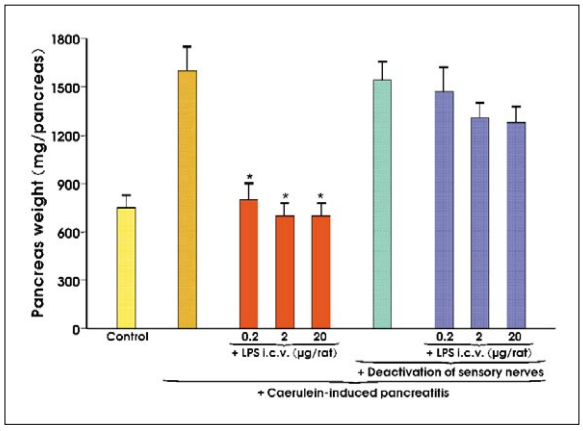

Figure 1. Effect of increasing doses of LPS, given intracerebroventricularly (i.c.v.) on pancreatic weight in rats with intact or capsaicin deactivated sensory nerves subjected to caerulein-induced pancreatitis. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6-8 rats in each experimental group. Control = rats infused with saline.

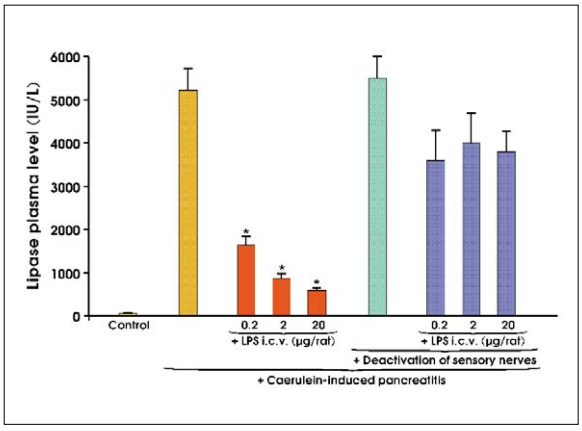

Figure 3. Effect of LPS, given intracerebroventricularly (i.c.v.) on plasma lipase level in rats with intact or capsaicin deactivated sensory nerves subjected to caerulein-induced pancreatitis. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6-8 rats in each experimental group. Control = rats infused with saline.

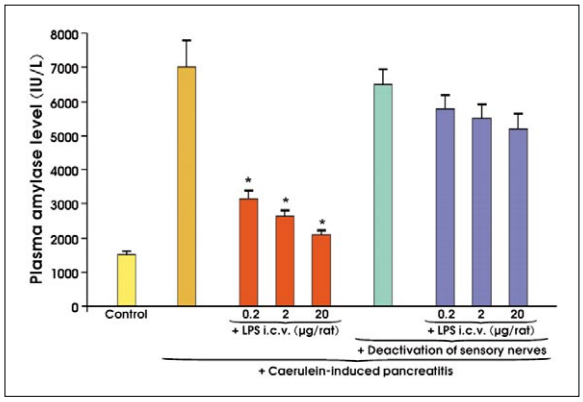

Figure 2. Effect of LPS, given intracerebroventricularly (i.c.v.) on plasma amylase level in rats with intact or capsaicin deactivated sensory nerves subjected to caerulein-induced pancreatitis. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6-8 rats in each experimental group. Control = rats infused with saline.

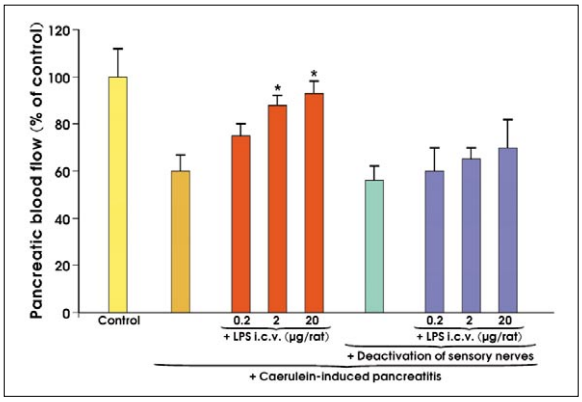

Figure 4. Pancreatic blood flow in response to LPS given intracerebroventricularly (i.c.v.) to rats with caerulein-induced pancreatitis with intact or capsaicin deactivated sensory nerves. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6-8 rats in each experimental group. Control = rats infused with saline.

using a Laserflo, model BPM 403 A (Blood Perfusion Monitor, Vasdamedics Inc. St Paul, Mn, USA) as previously described [10]. Blood flow was measured in five different pancreatic regions in each rat and expressed as the percent change of the control value. Immediately afterwards blood was drawn from the inferior vena cava for plasma measurement of amylase, lipase, interleukin-10 (IL-10) and leptin. Plasma amylase was measured with the modified sacharogenic method using Alpha Diagnostics kit as described elsewhere [10]. Lipase was measured using an automatic analyser Kodak Ektachem with slides (Lipa). Leptin was measured by radioimmunoassay (RIA) with commercial RIA kit (LINCO Research Inc. St. Charles, Missouri, USA). Plasma IL-10 was measured with the ELISA method (Enzyme Linked Immuno-Sorbent Assay) using the kit of Bio-Source International, Camarillo, California, USA.

The pancreas was then excised, connective and fat tissue was removed and the pancreas was weighed. Pancreatic samples were fixed in 10% formalin and then stained with hematoxylin and eosin for histological study. The specimen was studied under an optic microscope and edema, polynuclear cell infiltration and vacuolization were graded on a scale from 0 to 3 i. e. from absent to severe lesion.

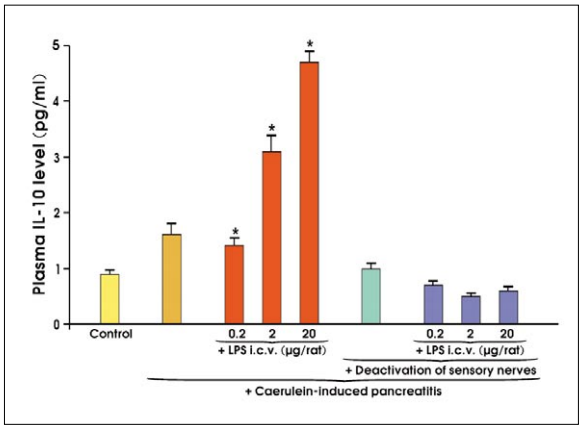

Figure 5. Effect of LPS given intracerebroventricularly on leptin plasma level in rats with caerulein-induced pancreatitis with intact or capsaicin deactivated sensory nerves. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6–8 rats in each experimental group. Control = rats infused with saline.

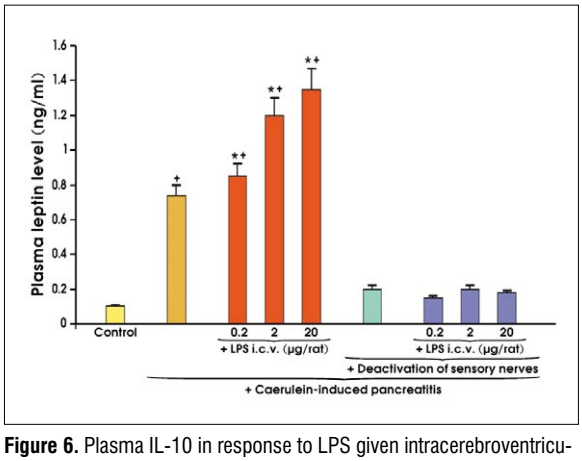

Figure 6. Plasma IL-10 in response to LPS given intracerebroventricularly (i.c.v.) to rats with caerulein-induced pancreatitis with intact or capsaicin deactivated sensory nerves. Asterisk indicates a significant ($p<0.05$) decrease below the value obtained from rats subjected to caerulein-induced pancreatitis without LPS pretreatment. Means±SEM of 6-8 rats in each experimental group. Control = rats infused with saline.

Statistical analysis

Analysis of variance and Student's t-test were used to analyze the results. A $p<0.05$ was considered as significant. The results were expressed as means±SEM

RESULTS

Acute caerulein-induced pancreatitis (CIP) was observed in all experimental animals, which were given caerulein. CIP was characterized by an almost double increase in the pancreatic mass, which is an indicator of pancreatic edema, a significant increase in plasma levels of amylase and lipase and in a reduction of pancreatic blood flow to 60% of the control value (Figures 1–5). Histologically,

Table 1. Histological changes induced by caerulein-induced pancreatitis (CIP) alone, intracerebroventricular administration of LPS (0.2, 2, or 20 mg/rat) alone, or combination of above in rats with intact sensory nerves. Asterisk indicates a significant change as compared with CIP alone.

	Edema (0-3)	Neutrophile infiltration (0-3)	Vacuolization (0-3)
Control	0	0	0
Caerulein-induced pancreatitis (CIP)	2.2±0.05	2.0±0.2	2.6±0.1
Caerulein-induced pancreatitis + LPS i.c.v. 0.2 mg/rat	1.6±0.2	1.8±0.1	1.6±0.2
Caerulein-induced pancreatitis + LPS i.c.v. 2 mg/rat	1.0±0.1*	0.86±0.2*	1.1±0.1“
Caerulein-induced pancreatitis + LPS i.c.v. 20 mg/rat	0.6±0.05*	0.7±0.2*	1.0±0.05*
LPS i.c.v. 0.2 mg/rat	0.2±0.1	0	0
LPS i.c.v. 2 mg/rat	0.2±0.05	0	0
LPS i.c.v. 20 mg/rat	0	0	0

Table 2. Histological changes induced by caerulein-induced pancreatitis (CIP) alone,intracerebroventricular administration of LPS (0.2, 2, or 20 mg/rat) alone, or combination of above in the rats with sensory nerves deactivated with capsaicin (INC). Asterisk indicates significant change as compared with CIP alone.

	Edema (0-3)	Neutrophile infiltration (0-3)	Vacuolization (0-3)
Control INC	0	0	0
Caerulein-induced pancreatitis - INC.	2.5±0.1	2.0±0.2	2.1±0.1
Caerulein-induced pancreatitis + LPS i.c.v. 0.2 mg/rat INC	2.3±0.2	2.0±0.1	1.8±0.3
Caerulein-induced pancreatitis + LPS i.c.v. 2 mg/rat INC	2.50±0.1	2.2±0.4	2.2±0.1
Caerulein-induced pancreatitis + LPS i.c.v. 20 mg/rat INC	2.1±0.1*	1.8±0.2	2.0±0.1
LPS i.c.v. 0.2 mg/rat INC	0.2±0.1	0	0
LPS i.c.v. 2 mg/rat INC	0.1±0.05	0	0
LPS i.c.v. 20 mg/rat INC	0	0	0

intralobular and intraalveolar edema, polynuclear cell infiltration and vacuolization of acinar cells were seen (Table 1, Fig. 7). Plasma IL-10 in rats with CIP doubled and leptin increased almost 7-fold as compared to the control animals without CIP (Fig. 5 and 6).

Administration of LPS to the cerebral ventricles (0.2, 2 or 20 µg/rat) resulted in a significant decrease in the pancreatic mass (Fig. 1). Histologically, inflammatory changes were significantly attenuated i. e. edema was almost completely abolished, and inflammatory infiltration and vacuolization were markedly diminished (Table 1, Fig. 7).

Plasma levels of amylase and lipase were dramatically decreased in CIP rats pretreated with i.c.v. LPS (Figs 2 and 3). Pancreatic blood flow in CIP rats receiving LPS intracerebroventricularly was increased in a dose-dependent manner, achieving almost 100% of the con-

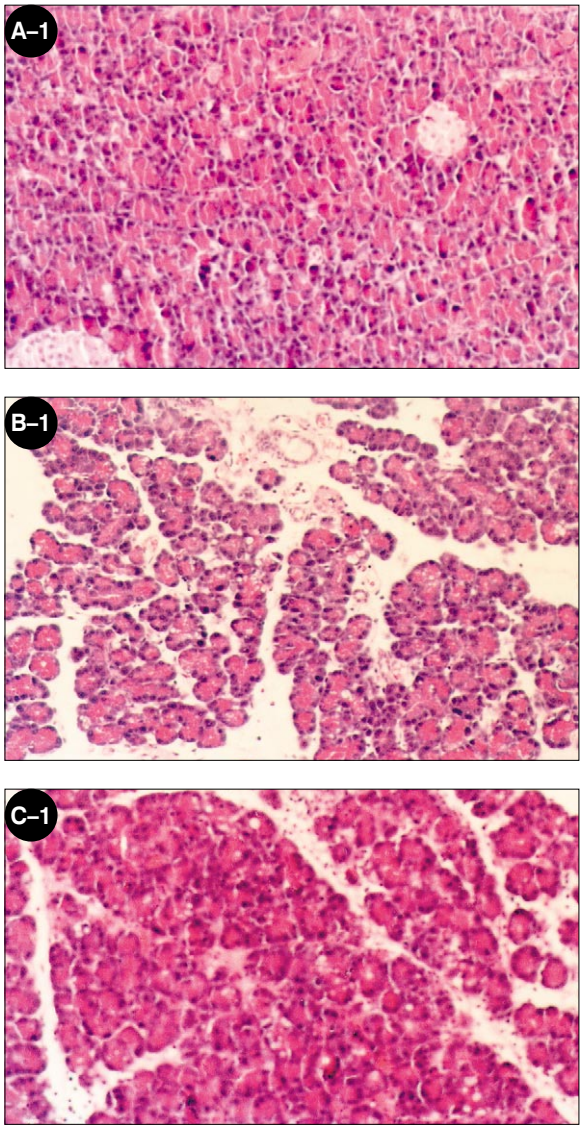

Figure 7. Histological section of pancreas from intact rats (A-1), severe edema, infiltration and cell vacuolization in the pancreas of rats subjected to caerulein-induced pancreatitis (B-1), and mild inflammatory changes represented by reduced edema and neutrophil infiltration in the pancreas of rats with CIP pretreated with LPS (20 μg/rat i.c.v.) (C-1). Hematoxylin-eosin stain, magnification 165x.

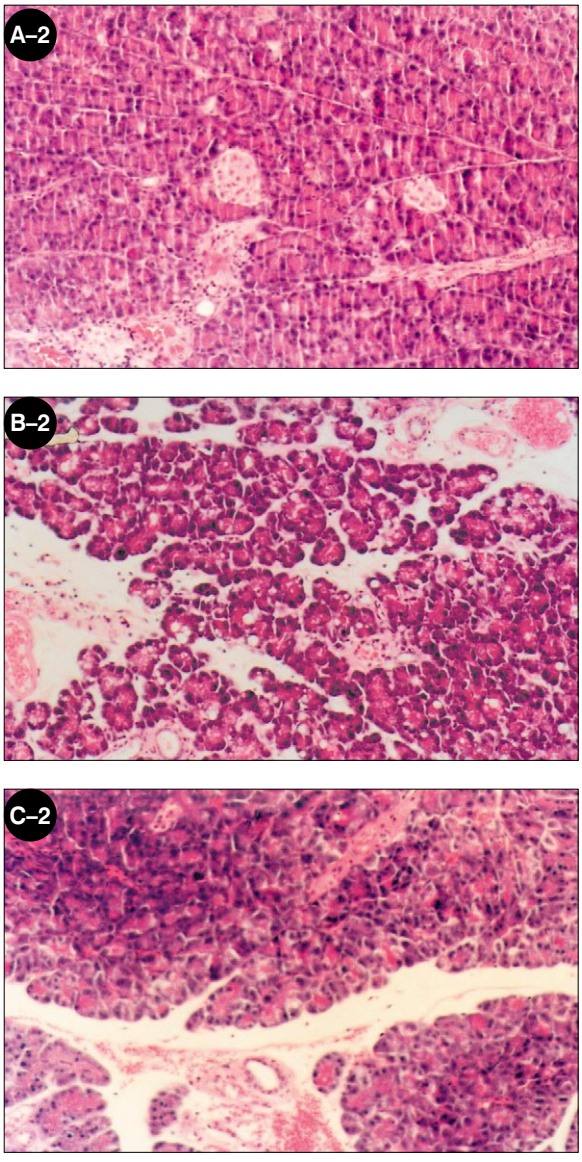

Figure 8. Deactivation of sensory nerves with capsaicin failed to affect the histological appearance of pancreas (A-2), severe edema, infiltration and cell vacuolization in the pancreas of capsaicin-pretreated rats subjected to caerulein-induced pancreatitis (B-2), intracerebroventricular administration of LPS (20 μg/rat i.c.v.) failed to affect significantly the inflammatory changes produced by caerulein-induced pancreatitis in the pancreas of rats with capsaicin-deactivated sensory nerves (20 μg/rat i.c.v.) (C-2). Hematoxylin-eosin stain. Magnification 165 x.

trol value at a dose of 20 μg/rat (Fig. 4). Anti-inflammatory IL-10 in CIP rats pretreated with LPS increased markedly as compared to the level obtained in CIP animals without LPS. Intracerebroventricular administration of LPS at a dose of 2 μg/rat to the CIP rats resulted in double increase of plasma level of IL-10, and following i.c.v. pretreatment of CIP rats with LPS at dose of 20 μg/rat plasma level of this interleukin increased more than 3-fold as compared to IL-10 level obtained in animals subjected to CIP alone (Fig. 5).

Plasma leptin level in rats pretreated with LPS given i.c.v. with subsequent CIP was further increased as compared to the animals with CIP alone (Fig. 6). Administration of LPS i.c.v. at a dose of 20 μg/rat doubled plasma leptin level as compared to CIP animals without LPS pretreatment (Fig. 6).

In rats with sensory nerves deactivated with capsaicin, administration of caerulein (5 μg/kg-h x 5 h) to induce CIP, did not produce significant differences in edema severity, morphology of pancreatic tissue, pancreatic blood flow or plasma amylase or lipase, as compared to CIP animals with intact sensory nerves (Figs 1–8, table 2).

Inactivation of sensory nerves by capsaicin resulted in complete abolition of the protective effects of LPS (0.2, 2 or 20 μg/rat i.c.v.) on the pancreas of CIP rats (Figs 1-6, 8 Table 2). In these animals marked pancreatic edema, high plasma levels of amylase and lipase and reduced pancreatic blood flow were observed (Figs 1-3). Above reversion of the favorable effect of LPS on the pancreas of CIP rats with inactivated sensory nerves was confirmed by histological examination of the pancreatic tissue (Table 2, Fig. 8).

In the rats with capsaicin-deactivated sensory nerves subjected to CIP plasma level of IL-10 was reduced, as compared to the plasma level of this interleukin observed in the CIP rats with intact sensory nerves. Central administration of LPS to the CIP rats with sensory nerves deactivated with capsaicin failed to affect significantly this low plasma level of IL-10 (Fig. 6).

Deactivation of sensory nerves caused an abrupt fall of plasma leptin in CIP animals as compared to the level measured in CIP animals with intact sensory nerves. LPS administration to above animals did not produce any significant alteration of plasma leptin levels (Fig. 7).

Discussion

In this study we investigated whether bacterial LPS applied centrally may affect the course of acute pancreatitis induced by overstimulation of the pancreas with caerulein and if so by what could be the mechanism of this effect. .

It was previously demonstrated that cerebral centers play an important role in the regulation of exocrine pancreatic secretion [21,22,24]. Dorsal vagal complex (DVC) has been recently identified as the main center responsible for the control of pancreatic enzymes secretion though activation of sympathetic nerves and adrenal gland [25]. However, no reports have been published concerning the involvement of brain centers in the modulation of the inflammatory processes in the pancreas.

Our study clearly demonstrates that LPS from *Escherichia coli* applied centrally to CIP rats are able to produce almost complete reversion of inflammatory changes produced by caerulein overstimulation in the pancreas of CIP rats. In CIP rats pretreated intracerebroventricularly with LPS significant reduction of pancreatic edema, decreased plasma levels of lipase and amylase and normalization of pancreatic blood flow, which was formerly limited by acute inflammation, was observed. The effect of LPS reducing the development of acute pancreatitis largely depends on the activation of sensory nerves, because deactivation of these nerves by capsaicin completely abolished favorable effects of LPS on the pancreas. It has been hypothesized that these sensory nerves originating in the pancreas transmit impulses to vagal centers in medulla and then act on the pancreas through efferent autonomic nerves and various neuromediators such as leptin, CGRP, VIP etc.

Previous reports, including those from our laboratory, have demonstrated that intraperitoneal administration of small doses of bacterial endotoxins from Escherichia coli prior to acute pancreatitis activated immune mechanisms and reduced pancreatic tissue injury [9,10]. Favorable effects of LPS, alleviating acute pancreatitis are mainly associated with increased generation of nitric oxide (NO), whereas high doses of LPS given to experimental animals aggravate the inflammatory process in the pancreas [8,10,26].

Acute pancreatitis activates a variety of pathogenic mechanisms by which pancreatic injury occurs, such as the generation of reactive oxygen and nitrogen species, reduction in pancreatic blood flow, accumulation of pro-inflammatory cytokines [5,27–30]. In parallel with injury factors immune mechanisms are mobilized, which include increased generation of NO, endogenous prostaglandins or antioxidants, which act to reduce the inflammatory state and tissue injury [3,28,31]. The severity of acute pancreatitis depends on injury factor, occurring in the course of inflammation and on the mobilization of immune mechanisms. The latter are a subject of extensive experimental and clinical studies, but until now it is not known which factors play a key role in pancreatic protection.

Present findings have indicated that pancreatoprotective effect of centrally applied LPS is associated with the release of leptin and depends on the activation of sensory nerves. Leptin is produced in adipose cells and peritoneal organs, such as the stomach and pancreas, and is known to regulate food intake and energy expenditure [32] However, recent studies have indicated that plasma leptin levels could be markedly stimulated by bacterial endotoxins [13–15]. A significant increase of leptin release have been observed in the early stage of inflammation [33, 35]. Numerous studies have indicated that leptin is involved in the modulation of immune response of the organism through activation of macrophages, effect on lymphocytes and cytokines [18,23,36–38]. Because of the contribution of leptin to the inflammatory process and similarity between the structure of leptin receptor and interleukin receptor (IL-6, IL-11, GCSF) leptin is classified as a cytokine [34].

As shown in our previous studies leptin is able to protect the pancreas against the injury caused by acute inflammation [17,20]. Above beneficial effects of leptin are mediated by sensory nerves [20]. Because of the presence of leptin receptors on pancreatic neurons leptin was though to be involved in the modulation of signals transmission in pancreatic nerves acting as a neuromodulator [39]. The observation that leptin could affect the synaptic activity of pancreatic neurons supports this notion [40].

Recent studies have demonstrated that pancreatoprotective effect of leptin is also associated with increased generation of NO. It was found that leptin released locally in the pancreas could affect gene expression of constitutional nitric oxide synthase and could stimulate NO release from pancreatic acini [18,20,]. This NO of

pancreatic origin, by penetrating the surrounding tissues, may lead to the relaxation of blood vessels. This improves the haemodynamic conditions in the inflammatory pancreas and limit the pancreatic tissue injury. Recent studies have demonstrated that leptin could produce relaxation of blood vessels on different ways, and its vasoactive effect depends on the increased generation of NO, as well as on the others, yet undefined, mechanisms independent on nitric oxide [41,42].

Acute pancreatitis leads to the activation of inflammatory cells, macrophages and lymphocytes and to increased release of cytokines involved in the regulation of immune responses [5,43]. Blood level of pro-inflammatory cytokines increases (IL-1, IL-6, IL-8, TNFα) with simultaneous decrease in anti-inflammatory interleukins such as IL-4 or IL-10 [27,43,44]. Our recent studies on pancreatoprotective effects of leptin have demonstrated that leptin could modify the cytokine production in acute pancreatitis, leading to the decrease of pro-inflammatory TNFα, with concomitant rise of anti-inflammatory IL-4 in the plasma [17]. In the present study we analyzed the relationship between central administration of LPS and blood levels of leptin and anti-inflammatory IL-10. Previous studies have demonstrated that anti-inflammatory IL-10 is able to inhibit the production of pro-inflammatory cytokines such as TNFα, IL-6 or IL-8 [45]. According to the recent findings, IL-10 could attenuate the course of pancreatitis or prevents the pancreas from acute inflammation [5,31]. In present study we found a close correlation between leptin release by LPS and an increase in plasma level of IL-10. Inactivation of sensory nerves by capsaicin leads to complete reversal of favorable effects of LPS on the pancreas and it also decreases blood leptin levels.

Studies on the role of leptin in the digestive system have demonstrated that endogenous leptin may be produced in the gastric mucosa and in the pancreas [16,18,46]. Administration of exogenous leptin protects gastric mucosa against acute lesion through a mechanism associated with the activation of arginine-NO system and stimulation of CCK release [16]. It has been shown that low dose of bacterial LPS exerts gastroprotective and pancreatoprotective effects leading to increased generation of NO [10,11]. These beneficial effects of LPS on the pancreas resembles those exerted by leptin [17,18]. However, the relationship between central administration of LPS, leptin release and pancreatic protection has not been studied until now.

CONCLUSIONS

The present study demonstrates that administration of LPS by the intracerebroventricular route limits the development of acute pancreatitis and reduces pancreatic injury. The alleviation of pancreatitis by LPS is accompanied by increased blood level of anti-inflammatory IL-10 and this effect may be mediated by the activation of sensory nerves and release of leptin by LPS.

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